

## **REMARKS**

### **I. Preliminary Remarks**

The Claims were subject to a Restriction Requirement, mailed September 28, 2006. Applicants acknowledge and appreciate the rejoinder of Groups I and II, which results in claims 1-18 being under examination.

After entry of this paper, Claims 5-12, and 16-17 are original. Claims 1-4, 13-15, and 18 are amended. Claims 19-28 are withdrawn, with claims 19, 21, and 27 being withdrawn and currently amended. Withdrawn claims are withdrawn without prejudice in an effort to favorably advance prosecution of the present application. Applicant reserves the right to pursue the subject matter of the withdrawn claims in a continuing application, or to have the withdrawn claims rejoined in the current application. Support for the amendments to the claims is found throughout the specification. The amendments do not include new matter. Reconsideration and withdrawal of the rejections are solicited for the reasons set out below.

In this response, Applicant addresses each of the rejections raised by the Examiner. Applicant therefore respectfully submits that the present application is in condition for allowance. Favorable consideration of all pending claims is respectfully requested.

This Response is timely filed, with a one-month extension of time. The USPTO is given authorization to charge Deposit Account No. 16-1445 for any fees necessary with the submission of this Response.

### **II. Patentability Arguments**

#### **A. The Anticipation Rejection of Claims 1-2, and 18 Under 35 U.S.C. §102(b) May Properly be Withdrawn.**

A patent is invalid for anticipation under 35 USC 102(b) if a single prior art reference identically discloses each and every limitation of the invention as set forth in the claims. (Lewmar Marine, Inc. v. Barient, Inc., 827 F.2d 744, 747 (Fed. Cir. 1987)). The prior publication must disclose in an enabling manner the invention that is in question. The exclusion of a claimed element, no matter how insubstantial or obvious, from a reference is enough to negate anticipation. (Connell v. Sears, Roebuck & Co., 220 U.S.P.Q. 193, 1098 (Fed. Cir. 1983)). Applicant respectfully submits that these criteria are not met in the Examiner's rejection. The claims, therefore, are not anticipated by the references.

The Examiner has rejected claims 1, 2, and 18 under 35 U.S.C. 102(b) as being anticipated by Lipson, et al., US 2002/0010203 (Appl. No. 09/741,842). Applicants respectfully traverse this rejection.

The Examiner states that "The claim limitation "substantially free of polymorph I [or II]" has no patentable weight, because the claim is drawn to "a compound." As a result the disclosure of the compound anticipates claims 1 and 2." However, claims 1, 2, and 18 have been amended to be drawn to a polymorph form of a compound of formula I, which renders this rejection moot.

As stated above, a rejection of a claim for anticipation requires that the single cited reference disclose each and every element of the claim in an enabling manner. Lipson, et al., do not anticipate the claimed invention because they fail to disclose each and every element of the claim in an enabling manner. Lipson, et al., do not describe or enable polymorphs of a compound of formula I.

The Examiner states that "for a known compound with defined chemical nature to be patentable for a new form, it must have a patentability basis for an advantage in terms of stability, formulation, solubility, bioavailability, ease of purification, preparation or synthesis, hygroscopicity, recovery, prevention of precipitation, etc. The instant claims differ from the known product merely by forms and the physical properties innate to the forms."

However, the analysis of the dissolution rates and the thermodynamic stability provided surprising and unexpected results. It is stated in the specification that "the IDR (intrinsic dissolution rate) of polymorph II is about three times of apparent IDR of polymorph I in pH 2 buffer at 23°C (Table C). This result contradicts the earlier observation that polymorph II is less stable and expected to have a lower solubility and therefore, a lower IDR at the same temperature and in the same solvent." (page 19, paragraph 0057) Also, differential scanning calorimetry showed different melting points and different enthalpy of melting for the polymorphs. It is stated in the specification that "The melting point of polymorph II is about 3°C higher than that of polymorph I. Therefore, polymorph II is the thermodynamically more stable polymorph near melting temperature. The higher melting point polymorph II also has a higher enthalpy of melting." (page 22, paragraph 0063) Finally, a slurry conversion experiment showed the relative thermodynamic stability relationship

between the two polymorphs. It is stated in the specification that the data suggest that polymorph II is thermodynamically more stable than polymorph I at room temperature. Because polymorph II is also more stable near melting temperature, the two polymorphs are monotropically related, i.e. polymorph II is more stable from room temperature to melting temperature.” (page 24, paragraph 0068)

It is surprising and unexpected that polymorph II would have both a higher melting point and a more rapid dissolution rate. One would expect the form with the higher melting point to be more stable and thus have a slower dissolution rate. The faster dissolution rate of polymorph II would provide enhanced bioavailability. The higher stability at room temperature through melting point would suggest better stability during manufacturing and longer shelf life of the composition.

Thus, based on the remarks presented herein, the rejection of claims 1, 2, and 18 under 35 U.S.C. 102(b) is overcome. Withdrawal of the rejection is therefore respectfully requested.

**B. The Obviousness Rejection of Claims 3-17 Under 35 U.S.C. §103(a) May Properly be Withdrawn.**

The Examiner stated that “This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a).” The following is a quotation of 35 U.S.C. 103(c)(1):

Subject matter developed by another person, which qualifies as prior art only under one or more of subsections (e), (f), and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the claimed invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 3-17 are rejected under 35 U.S.C. 103(a) as being obvious over Tang, et al., US 6,573,293. Applicants respectfully traverse this rejection.

All of the inventors of the instant application were employed by Pharmacia & Upjohn Company (hereinafter P&U) at the time the claimed invention was made. It is a general practice of P&U that employees are bound by an employment agreement that states, *inter alia*, that any confidential information, trade secrets, improvements, and inventions conceived or reduced to practice by the Employee and all rights with respect thereto, relating

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to the business, processes, apparatus, products, researches or research programs of P&U, shall be the sole and exclusive property of P&U, and that the Employee shall assign to P&U the entire right and title to said improvements and inventions, and any US and foreign patent applications and patents covering same.

The inventors of the instant application specifically assigned their entire right, title and interest in the invention or inventions, all improvements and modifications thereof, all applications for said invention(s), and all divisions, continuations, reissues, and extensions of said applications and Letters Patent to P&U. The assignment was executed by Changquan (Calvin) Sun on July 25, 2003; Todd P Foster on August 4, 2003; Fusen Han on August 11, 2003; Michael Hawley on July 24, 2003; and Tom Thamann on August 4, 2003. The assignment was recorded at the United States Patent and Trademark Office on August 13, 2003 at (reel/frame) 014379/0084.

The US 6,573,293 patent is assigned to both Sugen, Inc. (hereinafter Sugen) and P&U. P&U purchased Sugen including all assets, in 1999, making Sugen was a wholly owned entity of P&U. Thus, at the time the invention claimed in the current application was made, P&U owned the entire right, title, and interest in the technology that eventually became US patent 6,573,293. Nine of the ten inventors specifically assigned their entire right, title and interest in the invention or inventions, all improvements and modifications thereof, all applications for said invention(s), and all divisions, continuations, reissues, and extensions of said applications and Letters Patent to Sugen. The assignment was executed by Peng Cho Tang on October 28, 2001; Todd A. Miller on October 23, 2001; Xiaoyuan Li on October 30, 2001; Li Sun on October 22, 2001; Chung Chen Wei on October 29, 2001; Shahrzad Shirazian on October 30, 2001; Congxin Liang on October 29, 2001; Tomas Vojkovsky on October 30, 2001; and Asaad S. Nematalla on October 29, 2001. The tenth inventor specifically assigned his entire right, title and interest in the invention or inventions, all improvements and modifications thereof, all applications for said invention(s), and all divisions, continuations, reissues, and extensions of said applications and Letters Patent to P&U. The assignment was executed by Michael Hawley on October 26, 2001. The assignment for all inventors was recorded at the United States Patent and Trademark Office on November 15, 2001 at (reel/frame) 012310/0844.

Based on these remarks, US patent 6,573,293 is disqualified as a 35 U.S.C. 103(a) reference, and the rejection of claims 3-17 under 35 U.S.C. 103(a) is overcome. Withdrawal of this rejection is therefore respectfully requested.

**C. The Enablement Rejection of Claims 3-12 under 35 U.S.C. §112, First Paragraph May Be Properly Withdrawn.**

To satisfy the requirement under 35 U.S.C. §112, first paragraph, the application as filed must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. *Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111 (Fed. Cir. 1991); *see also* M.P.E.P. §2163 (I). The initial burden of establishing a *prima facie* case of lack of written descriptive support is on the Office. M.P.E.P. §2163 (II). There is a strong presumption that an adequate written description of the claimed invention (i.e., the claims) is present when the application is filed. *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976); *see also* M.P.E.P. §2163 (I)(A).

Claims 3-12 are rejected under 35 U.S.C. 112, first paragraph, as containing “subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.” Applicants respectfully traverse this rejection.

(I) The Examiner states that “the data provided in Claims 3 and 4 is not sufficient to distinguish the polymorph forms I and II from the compound and other polymorphs.” Applicants respectfully traverse this rejection.

As stated in the M.P.E.P. § 2163:

[a]n applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. *Enzo Biochem*, 323 F.3d 956, 964 (Fed. Cir. 2002).

Provided in Claims 3 and 4 are the five strongest peaks from the PXRD patterns for polymorph form II (claim 3) and polymorph form I (claim 4). Only one peak is similar between the PXRD patterns of the two polymorphs. Within the disclosure, the Applicants have fully defined polymorphs (see paragraphs 0042-0046); described how to make

polymorph I (see paragraphs 0106 and 0107) and polymorph II (see paragraph 0108); described the analytical methods for determination of the identity and physical properties of the polymorphs, including 1) estimation of the solubility of a polymorph in various solvents, 2) determination of the pH-solubility profile, 3) PXRD diffraction, 4) Differential Scanning Calorimetry, 5) Polarized light Microscopy, 6) Fourier-Transformed Infrared Spectroscopy, 7) Fourier-Transformed Raman Spectroscopy, and 8) Rotating Disc Intrinsic Dissolution Rate (see paragraphs 0058-0075); and presented the results of these methods (see paragraphs 0077-0104). As demonstrated in the results, the intrinsic dissolution rate of polymorph II is three times that of polymorph I (see paragraph 0088). Two distinctive PXRD patterns were observed in two batches of 5-[5-fluoro-2-oxo-1,2-dihydroindol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-pyrrolidin-1-ylethyl)-amide (see paragraph 0091 and figure 1). In addition, spectral variations are clearly observed in the IR and RAMAN spectra data for the two forms (see paragraphs 0093 and 94 and figures 2 and 3). Finally, the polarized light microscopy (paragraph 0096) and DSC (paragraph 0099) demonstrated differences between polymorphs I and II.

It is well settled that the definiteness of a claim is not judged in a vacuum. Instead the claim must be viewed in the context of the disclosure of the application from which it is derived. The test for definiteness is whether one skilled in the art would understand the bounds of the claim when read in light of the specification. Orthokinetics, Inc. v. Safety Travel Chairs, Inc., 806 F.2d 1565, 1 USPQ2d 1081 (Fed. Cir. 1986). See also BJ Services Co. v. Halliburton Energy Services, Inc. 338 F.3d 1368, 1372, 67 USPQ2d 1692, (Fed. Cir. 2003): "The question becomes whether one of ordinary skill in the art would understand what is claimed when the claim is read in light of the specification." Given the explicit teachings of the specification referred to above with respect to the characteristics of polymorphs I and II, the Applicants submit that one skilled in the art, upon reading the specification, would clearly be able to distinguish polymorphs I and II.

(2) The Examiner states that "Claims 5-12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. ... The specification of the instant application fails to describe how the polymorph of claim 1 will be maintained in a pharmaceutical composition." Applicants respectfully traverse this rejection.

As stated in the MPEP (see section 608.01(p)1.A.):

“An application for a patent when filed may incorporate “essential material” by reference to (1) a U.S. patent, or (2) a U.S. patent application publication, which patent or patent application publication does not itself incorporate such essential material by reference. See 37 CFR 1.57(c). Prior to October 21, 2004, Office policy also permitted incorporation by reference to a pending U.S. application.”

As provided in the specification of the instant application (see paragraph 0047), “Carriers and excipients for the formulation of pharmaceutically acceptable compositions comprising the polymorphs of the preferred embodiments of the present invention are well known in the art and are disclosed, for example, in U.S. patent application Ser. No. 09/783,264, filed February 15, 2001, which is incorporated herein in its entirety. See WO 01/60814.” The terms “physiologically/pharmaceutically acceptable carrier” and pharmaceutically acceptable excipient” are defined in Application 09/783,264, which issued as US patent 6,573,293, (see column 14, lines 12-23). Further discussion of pharmaceutical compositions is found at column 171, line 3 through column 174, line 7. Given the explicit teachings of the specification referred to above with respect to the pharmaceutical compositions, the Applicants submit that one skilled in the art, upon reading the specification, would clearly be able to formulate polymorphs I and II.

In view of the foregoing, Applicants respectfully submit that one skilled in the art can make and use the claimed vaccine without undue experimentation. There is written description support for claims 3-12. The rejection of claims 3-12 under 35 U.S.C. §112, first paragraph, is thus overcome. Withdrawal of this rejection is respectfully requested.

**D. The Indefiniteness Rejection of Claims 1-4 under 35 U.S.C. §112, Second Paragraph May Be Properly Withdrawn.**

Claims 1-4 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants respectfully traverse this rejection.

The Examiner states that claims 1 and 2 are indefinite for failing to provide the meets and bounds of the claims. Claim 1 has been amended to include the phrase “wherein the polymorph form is the polymorph II form” (see claim listing above), Claim 2 has been amended to include the phrase “wherein the polymorph form is the polymorph I form” (see

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claim listing above). These amendments render this rejection moot. It is respectfully submitted that a person of ordinary skill in the art would understand these claims in view of the claim amendments and the specification of the instant application. Applicants respectfully request withdrawal of this rejection.

The Examiner states that "Claims 3 and 4 are indefinite because they fail to meet the minimum standard for a powder X-ray diffraction pattern, and they fail to provide an alternative method for distinguishing the claimed polymorph over the others." The arguments provided in Section II.D. above apply here also. Given the explicit teachings in the specification referred to above with respect to the characteristics of polymorphs I and II, the Applicants submit that one skilled in the art, upon reading the specification, would clearly be able to distinguish polymorphs I and II. Applicants respectfully request withdrawal of this rejection.

### **III. Conclusion.**

In view of the amendments and remarks made herein, Applicants respectfully submit that Claims 1-18 are in condition for allowance and request expedited notification of same.

Respectfully submitted,

  
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